REMARKS

Favorable reconsideration is respectfully requested in view of the following remarks.

Claims 19-29 were pending in this application when last examined.

Claims 22-28 were withdrawn as non-elected subject matter.

Claims 19-21 and 29 were examined on the merits and stand rejected.

On pages 3-11 of the Office Action, claims 19-21 and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Huston et al. (US 2005/0255113) in view of Kuwako et al. (Kuwako et al., "Activation of calpain in cultured neurons over-expressing Alzheimer amyloid precursor protein", *Brain Res Mol Brain Res.* 107(2):166-75, 2002), Milton et al. (WO 2002/36614) and Findeis et al. (US patent 5,854,204). Applicants respectfully traverse this rejection.

Applicants note that the claimed invention is directed to a method for treating Alzheimer's disease, comprising administering an adeno-associated virus vector expressing β amyloid (hereinafter "Aβ") peptide in intestinal cells in a therapeutically effective amount to a subject, wherein the adeno-associated virus vector comprises DNA encoding said Aβ peptide and DNA encoding a signal peptide capable of extracellularly secreting said Aβ peptide, in an operative form.

In the claimed invention, the adeno-associated virus is used for administration to a subject. The adeno-associated virus has the interesting feature that it is not easily degraded by gastric juice (see page 8, lines 21 to 23), and thus the vector of the present invention can reach and infect intestinal cells efficiently.

Further, the vector of the present invention comprises "DNA encoding Aβ peptide" as well as "DNA encoding a signal peptide capable of extracellularly secreting Aβ peptide." The adeno-associated virus vector comprising "DNA encoding Aβ peptide" as well as the "DNA encoding a signal peptide" ensures secretion of Aβ peptide outside the intestinal cells so as to efficiently retain Aβ peptide as an antigen (see page 6, lines 1 to 5).

By using such adeno-associated vector to express Aβ peptide in intestinal cells, the claimed invention ensures primary induction of antibody production but only weak induction of a cellular immune response (see page 5, lines 32 to 36). As the result, the claimed invention

ensures reduction in amyloid deposition and senile plaque formation in the central nerve system without inflammation in the brain and other organs (see page 3, lines 22 to 26; page 14, line 5 to page 15, line 17; page 16, line 14 to page 18, line 1, and elsewhere). In particular, according to the claimed invention, not only intracellular amyloid plaques but also extracellular amyloid plaques are remarkably reduced (see Test 6, Table 1 and page 15, lines 18 to 22).

Further, the claimed invention causes a reduction in the concentration of TGF-β in the blood (see page 3, lines 26 to 27 and page 18, lines 2 to 19). It has been previously reported that TGF-β promotes Alzheimer's disease-related pathological changes such as cerebrovascular amyloid deposition and microvascular degeneration (see page 2, lines 21 to 29). Thus, the method of the claimed invention capable of reducing TGF-β in the blood is effective in reducing the progress of cerebrovascular amyloid deposition and microvascular degeneration of Alzheimer's disease (see page 3, lines 27 to 29).

On the other hand, Huston et al. (US2005/0255113) disclose an immunization of a subject with a DNA vaccine such as an adeno-associated vector encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), which provokes a host antibody immune response sufficient for inhibiting the formation of intracellular aggregates of the polypeptide. However, Huston et al. fails to disclose or suggest an adeno-associated virus vector comprising "DNA encoding Aβ peptide" itself and "DNA encoding a signal peptide." The APP secreted by the DNA vaccine of Huston et al. is a different antigen from the Aβ peptide itself. APP generates Aβ peptide when partially decomposed by enzymes in neural cells (see paragraph 0002, lines 6 to 8 of the present specification). Without decomposition in the cells, APP does not have the same antigenicity as Aβ peptide itself. According to the APP encoding DNA vaccine of Huston et al., APP would be directly secreted outside cells without decomposition since APP comprises a signal peptide. Thus, it is apparent to a person of skill in the art that the DNA vaccine of Huston et al. directly secreting APP outside the cells does not have the same antigenicity as the vector of the present invention secreting Aβ peptide itself. Thus, this reference fails to inherently teach or suggest the elements of the claimed invention as contended.

Further, Huston et al. fails to disclose or suggest that the adeno-associated virus vector expressing Aβ peptide in intestinal cells remarkably reduces intracellular and extracellular amyloid plaques. Also, Huston et al. fails to disclose or suggest that the adeno-associated virus vector expressing Aβ peptide in intestinal cells reduces the concentration of TGF-β in the blood.

Regarding Kuwako et al. (Mol Brain Res. 107(2): l67-75, 2002), this reference discloses construction of adenovirus vectors expressing APP and APPΔAβ20. However, Kuwako et al. fails to disclose or suggest an adeno-associated virus vector comprising "DNA encoding Aβ peptide" itself and "DNA encoding a signal peptide." Further, Kuwako et al. fails to disclose or suggest that adeno-associated virus vector expressing Aβ peptide in intestinal cells remarkably reduces intracellular and extracellular amyloid plaques. Also, Kuwako et al. fails to disclose or suggest that an adeno-associated virus vector expressing Aβ peptide in intestinal cells reduces the concentration of TGF-β in the blood.

Regarding Milton et al. (WO2002/36614), this reference discloses an antisense sequence of Aβ peptide residues 1 to 43 and fragments capable of binding to Aβ peptide (see, claim 1). However, Milton et al. fails to disclose or suggest an adeno-associated virus vector comprising "DNA encoding Aβ peptide" itself and "DNA encoding a signal peptide." Further, Milton et al. fails to disclose or suggest that an adeno-associated virus vector expressing Aβ peptide in intestinal cells remarkably reduces intracellular and extracellular amyloid plaques. Also, Milton et al. fails to disclose or suggest that adeno-associated virus vector expressing Aβ peptide in intestinal cells reduces the concentration of TGF-β in the blood.

Regarding Findeis et al. (US Patent 5,854,204), this reference discloses Aβ peptide residues 1 to 43 derivatives and sequences thereof (see column 64, Tables). However, Findeis et al. fails to disclose or suggest that an adeno-associated virus vector comprising "DNA encoding Aβ peptide" itself and the "DNA encoding a signal peptide." Further, Findeis et al. fails to disclose or suggest that an adeno-associated virus vector expressing Aβ peptide in intestinal cells remarkably reduces intracellular and extracellular amyloid plaques. Also, Findeis et al. fails to disclose or teach that an adeno-associated virus vector expressing Aβ peptide in intestinal cells reduces the concentration of TGF-β in the blood.

As mentioned Above, all of the cited documents fail to disclose or suggest the claimed adeno-associated virus vector comprising "DNA encoding Aβ peptide" itself and the "DNA encoding a signal peptide" as well as its advantageous effect attained when the vector is administered for expression in intestinal cells.

In summary, Huston fails to teach a vector which secretes Aβ peptide extracellularly but instead causes secretion of APP and therefore fails to teach secretion of the same antigen and its concurrently properties either inherently or expressly. Further, none of the cited references teach

both a DNA encoding Aβ peptide and a DNA encoding a single peptide. Also, none of the cited references teach that expressing such Aβ peptide in intestinal cells, which is an inherent property of the claimed invention, reduces both intracellular and extracellular amyloid plaques and reduces the concentration of TGF-β in the blood. Thus, the claimed invention is not rendered obvious by the cited art.

In addition, the present invention has led to ALZHEIMER'S DISEASE AWARD, 2005 presented by the Journal of Alzheimer's disease (see http://www.j-alz.com/award/award_2005.html). This award further indicates that one skilled in the art considers the present invention unexpected and remarkable.

Thus, for the above noted reasons, this rejection is untenable and should be withdrawn.

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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